PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 49324-294	**FOR FURTHER ACTION** See Form PCT/IPEA/416	
International application No. PCT/CA2004/000507	International filing date *(day/month/year)* 02.04.2004	Priority date *(day/month/year)* 02.04.2003
International Patent Classification (IPC) or national classification and IPC A61K9/127		
Applicant CELATOR TECHNOLOGIES INC.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01.02.2005	01.09.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Muller, S Telephone No. +31 70 340-2080

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/CA2004/000507

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-39	as originally filed
Claims, Numbers	
1-23	received on 30.07.2005 with letter of 29.07.2005
Drawings, Sheets	
1/16-16/16	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 22,23, with respect to industrial applicability

because:

☒ the said international application, or the said claims Nos. 22,23, with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 22,23, with respect to industrial applicability

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/CA2004/000507

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-23
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-23
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-21
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item I

Basis of the report

The attention of the Applicant is drawn to the fact that copper gluconate is mentioned in claim 18 as originally filed as $Cu(gluconate)_2$.
When amending the claims, the exact same expression should preferably be used in order to avoid any risk of infringment of Article 34(2)(b) PCT.

No basis in the Application as filed could be found for the new amended claims 20 and 21. Due to the absence of any evidence to the contrary, these claims are considered as introducing subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT.

The amendments as filed with the letter dated 29 July 2005 are therefore not acceptable under Article 34(2)(b) PCT.
However, in order to accelerate the procedure, the present IPER is based on claims 1-23 as filed with the letter dated 29 July 2005.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

For the assessment of the present claims 22,23 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. Cited Document

The following document D1 is referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: WO 02/28380 A (MARTIN CHRISTOPHE ; BAILEY SUSAN M (GB); TWELVES CHRISTOPHE J (GB); SQ) 11 April 2002 (2002-04-11)

2. Novelty (Article 33(2) PCT)

The present application appears to be new over the prior art, because no document of the prior art discloses liposomes that contain copper gluconate, said liposomes being stably associated with a water-soluble camptothecin and a fluoropyrimidine (Art. 33(2) PCT).

3. Inventive Step (Article 33(3) PCT)

D1 is considered as being the closest prior art. It discloses anti-tumor compositions comprising the fluoropyrimidine UFT (tegafur and uracil in a molar ratio 1:4), and folinic acid (leucovorin) to potentiate the coadministration of the water-soluble camptothecin irinotecan.

The current application differs from D1 in that the drugs are stably associated with liposomes.

The effect of this difference is a superior drug loading and sustained drug release of each agent. Synergistic ratios of these drugs, when encapsulated in liposomes, can be maintained over time in the blood compartment resulting in enhanced efficacy compared to the free drug cocktail (see page 3, paragraph 8).

The objective problem of the application may therefore be regarded as the provision of a composition for improved delivery of combinations of a water-soluble camptothecin and a fluoropyrimidine.

No document of the prior art suggests the use of liposomes for delivering combinations of fluoropyrimidine and camptothecin agents.
The application therefore appears to be inventive over the prior art (Article 33(3) PCT).

4. Industrial applicability

Claims 22,23 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).
Claims 1-21 satisfy the criterion of industrial applicability set forth in Article 33(4) PCT.

Application No.: PCT/CA2004/000507 Docket No.: 532552000740

Claims

1. A composition that comprises liposomes that contain copper gluconate, said liposomes being stably associated with at least one water-soluble camptothecin and at least one fluoropyrimidine at a camptothecin-to-fluoropyrimidine mole ratio that has a desired cytotoxic, cytostatic or biologic effect to relevant cells or tumor cell homogenates.

2. The composition of claim 1 wherein the desired cytotoxic, cytostatic or biologic effect to relevant cells or tumor cell homogenates is non-antagonistic.

3. The composition of claim 1 wherein said water-soluble camptothecin and fluoropyrimidine are co-encapsulated.

4. The composition of any of claims 1-3 which further includes leucovorin sufficient to stabilize said fluoropyrimidine.

5. The composition of any of claims 1-3 wherein the water-soluble camptothecin is irinotecan (CPT-11), topotecan, 9-aminocamptothecin or lurtotecan or wherein the water-soluble camptothecin is a hydrophilic salt of a water-insoluble camptothecin.

6. The composition of claim 5 wherein the water-soluble camptothecin is irinotecan (CPT-11) or topotecan.

7. The composition of any of claims 1-3 wherein the fluoropyrimidine is floxuridine, 5-fluorouracil (5-FU) or UFT (tegafur/uracil).

8. The composition of any of claims 1-3 wherein said water-soluble camptothecin is irinotecan and said fluoropyrimidine is floxuridine or 5-FU.

9. The composition of any of claims 1-3 wherein said liposomes comprise a phosphatidylcholine-containing lipid.

10. The composition of claim 9 wherein said phosphatidylcholine-containing lipid is DSPC or DAPC.

11. The composition of any of claims 1-3 wherein said liposomes comprise a phosphatidylglycerol or a phosphatidylinositol.

12. The composition of claim 11 wherein the phosphatidyl glycerol is DSPG or DMPG.

13. The composition of any of claims 1-3 wherein said liposomes comprise a sterol.

14. The composition of claim 13 wherein said sterol is cholesterol.

15. The composition of claim 14 wherein said cholesterol is present at less than 20 mol%.

16. The composition of claim 8 wherein said liposomes comprise DSPC, DSPG and cholesterol.

17. The composition of any of claims 1-3 wherein said liposomes contain triethanolamine (TEA).

18. The composition of any of claims 1-3 which, when administered to a subject, provides a therapeutic activity greater than that which is obtained when said water-soluble camptothecin and said fluoropyrimidine are administered in the same ratio but not stably associated with liposomes.

19. A method to prepare the composition of claim 2, which method comprises

a) determining in a relevant cell culture assay, cell-free assay or tumor cell homogenate assay for biological activity a mole ratio of said water-soluble camptothecin and fluoropyrimidine which is non-antagonistic over at least 5% of the concentration range over which greater than 1% of cells are affected ($f_a > 0.01$) by said ratio, and

b) encapsulating within said liposomes a mole ratio of water-soluble camptothecin-to-fluoropyrimidine determined to be non-antagonistic in step a).

20. The method of claim 19 wherein the encapsulating step b) comprises contacting liposomes containing copper gluconate and at least one fluoropyrimidine with said at least one water soluble camptothecin to effect uptake of said camptothecin.

21. The method of claim 19 wherein the encapsulating of step b) comprises contacting liposomes containing copper gluconate with said at least one water soluble camptothecin and said at least one fluoropyrimidine to effect uptake of said camptothecin and fluoropyrimidine.

22. A method to treat a disease condition in a subject which method comprises administering to a subject in need of such treatment a therapeutically effective amount of the composition of any of claims 1-3.

23. The method of claim 22 which further comprises administering leucovorin to said subject.